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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,517	08/01/2001	Michael F. Clarke	060173-0014 (UMIP-003)	6988

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,517	CLARKE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6,8-14,18-23,28-30,32,34,35,38,40,188,194 and 199-210* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 6, 8-14, 18-23, 28-30, 32, 34, 35, 38, 40, 188, 194, 199-210* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/27/04 has been entered.

The amendment and response filed on 8/27/04 has been entered. Claims 7, 24, 27, 33, 187 have been canceled by this amendment. Claims 1, 4, 6, 8-14, 18-23, 32, 34, 35, 38, 40, 188, 194, 199-204 have been amended. Claims 206-210 are newly submitted. Currently, claims 1, 4, 6, 8-14, 18-23, 28-30, 32, 34, 35, 38, 40, 188, 194, 199-210 are under examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 8/27/04 response would be addressed to the extent that they apply to current rejection.

Claim Objections

Claim 32 is objected to because the phrase "selected from the group consisting of" in (b) should not have been deleted.

Claim 194 is objected to because the phrase "solid tumor stem cells" should be inserted before "claim 23".

Claim 205 is objected to because the status of the claim as identified is incorrect.

Claims 34, 35, 38, 40, 188, 204, 210 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 6, 18, 19, 23, 28-30, 199, 201, 203, 207, 209 are rejected under 35 U.S.C. 102(b) as being anticipated by or alternatively under 35 U.S.C. 103(a) as being unpatentable over *Hathorn et al* (Cancer 1994;74:1904-11) or *Piselli et al* (Anticancer Res 2000;20:825-32), and as evidenced by *Janeway, Jr. et al* (Immunobiology, 1999) and *Thampoe et al* (Arch Biochem Biophys. 1988;267:342-52).

Hathorn et al teach a population of tumor cells isolated by fluorescence-activated cell sorter with an antibody recognizes CD44 (e.g. abstract, and table 4), wherein the tumor is renal carcinoma (solid tumor of epithelial origin). While not relied upon, *Janeway, Jr. et al* teach the recited CD markers (including CD24) are expressed in blood cells or endothelial cells (Appendix I), thus, the disclosed renal carcinoma tumor cells would intrinsically lack detectable levels of expression of the recited CD markers. Since the FACS sorting is capable of generating >95% purified population bearing markers of the selection antibody (anti-CD44), the end population would comprise less than 25% non-tumorigenic solid tumor cells (CD44-).

Likewise, *Piselli et al* teach a population of tumor cells isolated by fluorescence-activated cell sorter with an antibody recognizes CD44 (e.g. abstract, and figure 3), wherein the tumor is adenocarcinoma (solid tumor of epithelial origin). While not relied upon, *Janeway, Jr. et al* teach the recited CD markers (including CD24) are expressed in blood cells or endothelial cells (Appendix I), thus, the disclosed adenocarcinoma tumor cells would intrinsically lack detectable levels of expression of the CD markers.

Although the cited prior art does not teach the cell surface marker ESA, the marker appears to be associated with tumor cells of epithelial origin as evidenced by *Thampoe et al*, thus it appears to be an inherent characteristic of the renal carcinoma cells or adenocarcinoma cells. Alternatively, if the claimed tumor stem cells are not identical to the prior art tumor stem cells, then the existence of CD44, lack of surface CD markers, epithelial origin, and solid tumors are distinguishing characteristics in common between the prior art and instantly claimed cells. These common

characteristics would have reasonably suggested the existence of the same or similar type of epithelial solid tumor stem cells. Applicants are reminded that the office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the prior art products do not necessarily or inherently possess characteristics of claimed product, which requires factual evidence demonstrating that actual, unobvious differences exist or the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, the claimed invention as a whole was at least *prima facie* obvious, if not anticipated, by the references, in the absence of sufficient, clear and convincing evidence to the contrary.

Claim 199 is a product-by-process claim, the prior art cells differ from the claimed cells only by their method of manufacture. However, the claimed method of isolating/enriching the tumor stem cells would not distinguish them over the tumor stem cells taught by the prior art. See *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985), which teaches that a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products.

Please note that claim recitation, "[the solid tumor stem cell] in a culture medium comprises a Notch ligand" has not been given patentable weight in this rejection and

rejections that follow because it merely recites the surrounding of the tumor stem cells, whereas patentability of the cells are considered by the structure and function of the cells themselves.

Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Hathorn et al* (Cancer 1994;74:1904-11) or *Piselli et al* (Anticancer Res 2000;20:825-32), as applied to claims 1, 4, 6, 18, 19, 23, 28-30, 199, 201, 203, 207, 209 above, and further in view of *Salmon et al* (New Eng J Med 1978;298:1321-7).

The teaching of *Hathorn et al* or *Piselli et al* was discussed *supra*, *Hathorn et al* or *Piselli et al* do not teach to place tumor cells in the affixed substrate and/or to treat cells to reduce proliferation.

Salmon et al supplemented the teaching of *Hathorn et al* or *Piselli et al* by illustrating that these are routines in the process of investigating a solid tumor stem cell (table I), *Salmon et al* place tumor cells in a culture medium or affixed to 3% agar substrate (sections in page 1322), and observing the ability of tumor stem cells to give rise to new tumor cell colonies (tumorigenic). They go on to treat the tumor stem cells with drugs that inhibit cell growth (e.g. figure 1).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods by simply substituting the ovarian cancer cells as taught by *Salmon et al* with renal carcinoma or adenocarcinoma cells as taught by *Hathorn et al* or *Piselli et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because they are necessary steps of cancer investigation. For different type of tumors, the strategy of treatment may be different, and thus it is necessary to experiment on

different cell types. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Hathorn et al* (Cancer 1994;74:1904-11) or *Piselli et al* (Anticancer Res 2000;20:825-32), as applied to claims 1, 4, 6, 18, 19, 23, 28-30, 199, 201, 203, 207, 209 above, and further in view of *Salmon et al* (US 4,411,990, IDS/A1).

Claim 22 is drawn to solid tumor stem cells treated to increase proliferation.

The teaching of *Hathorn et al* or *Piselli et al* was discussed *supra*, *Hathorn et al* or *Piselli et al* (Anticancer Res 2000;20:825-32), do not teach to treat tumor cells to increase proliferation.

Salmon et al supplemented the teaching of *Hathorn et al* or *Piselli et al* by illustrating that it is routine and necessity in the process of investigating a solid tumor stem cell. *Salmon et al* teach adding nutrients such as METGF to the culture system to promote stem cell colony growth (column 4, lines 35-60) and to obtain sufficient number of cells for study.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method by simply substituting the ovarian cancer cells as taught by *Salmon et al* with renal carcinoma or adenocarcinoma cells as taught by *Hathorn et al* or *Piselli et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because they are necessary steps of cancer investigation. For different type of tumors,

the strategy of treatment may be different, and thus it is necessary to experiment on different cell types. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Hathorn et al* (Cancer 1994;74:1904-11) or *Piselli et al* (Anticancer Res 2000;20:825-32), as applied to claims 1, 4, 6, 18, 19, 201, 23, 28-30, 199, 203, 207, 209 above, and further in view of *Nierodzik et al* (Blood 1998;92:3694-3700).

Claims 8-13 are drawn to an isolated solid tumor stem cell contains a polynucleotide vector, preferably a plasmid, a reporter polynucleotide, and a recombinant polynucleotide The teaching of *Hathorn et al or Piselli et al* was discussed *supra*, *Hathorn et al* or *Piselli et al* do not teach tumor cells transfected with a heterologous gene.

Nierodzik et al supplemented the teaching of *Hathorm et al or Piselli et* by establishing that it is well known in the art to use tumor cells as a nucleic acid carrier encoding therapeutic agents (abstract). *Nierodzik et al* teach solid tumor stem cells transfected with an expression vector (pCDNA3) encoding a thrombin receptor (recombinant polynucleotide), and containing a reporter gene (Geneticin resistance with G418, see 1st paragraph, page 3695).

In view of such it would have been obvious for the ordinary skilled to transfect the tumor cells of *Hathorn et al or Piselli et al* with a nucleic acid expressing a therapeutic gene with a reasonable expectation of success. The ordinary skilled would have been

motivated to do so for tracking the tumor cells, and for cancer therapy. Thus, the claimed invention as a whole was *prima facie* obvious.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Hathorn et al* (Cancer 1994;74:1904-11) or *Piselli et al* (Anticancer Res 2000;20:825-32), as applied to claims 1, 4, 6, 8-13,18, 19, 201, 23, 28-30, 199, 203, 207, 209 above, and further in view of *Bromberg et al* (PNAS 1995;92:8205-9).

Claim 14 requires that the recombinant polynucleotide be integrated into a chromosome of the solid tumor stem cells.

Bromberg et al teach an isolated tumor stem cell derived from melanoma, transfected with a retroviral vector encoding a mutant extracellular TF, wherein the retrovirus would integrate into the chromosome of cells.

In view of such it would have been obvious for the ordinary skilled to transfect the tumor cells of *Hathorn et al or Piselli et al* with a retroviral nucleic acid expressing a therapeutic gene or a reporter gene with a reasonable expectation of success. The ordinary skilled would have been motivated to do so because a viral vector is more efficient for transfection. Given numerous vectors known in the art, this limitation falls within the bound of optimization. Thus, the claimed invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed. Claims 32, 34, 35, 38, 40, 188, 194, 200, 202, 204-206, 208, 210 appear to be free of the cited prior art of record, however, they are subject to other objection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Q. Janice Li
Primary Examiner
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QL
November 12, 2004